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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/549,296	09/15/2005	Ales Franc	J187-028US	1964

21706 7590 06/09/2008

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EXAMINER	
GEMBEH, SHIRLEY V	
ART UNIT	PAPER NUMBER
1614	

MAIL DATE	DELIVERY MODE
06/09/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/549,296	FRANC ET AL.	
	Examiner	Art Unit	
	SHIRLEY V. GEMBEH	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to restriction requirement

In the restriction, Applicant's election with traverse of claim 4 with the compound (OC-6-43)-bis(acetato)-(1-adamantylamine)-amine-dichloroplatinic complex as the elected specie in the reply filed on 1/29/08 is acknowledged. The traversal is on the ground(s) that a generic or at least a more generic claim might be found allowable than claim 4 alone and that claim 1 be added to the examination with newly added claims 20—25 if claim 4 is found allowable.

The request is granted and claims 1-25 are examined in this office action. The search is inclusive of JM216, thus extended beyond instant claim 4 specie election.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d).

Status of claims

Claims 1-25 are pending are examined in this office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 20-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims recite use the term functional **derivatives** of said groups, however, the Specification does not disclose these functional derivatives. It does disclose B and B'. However, the substituents of, B and B' do not embrace the broad subgenus nor does it provide structural guidance of these functional derivatives. Examiners understanding of a derivative is an infinite change in the function with respect to its' variables.

A lack of adequate written description issue arises if the knowledge and level of skill in the art would not permit one skilled in the art to immediately envisage the product claimed from the disclosed process. See, e.g., Fujikawa v. Wattanasin, 93 F.3d 1559, 1571, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (a "laundry list" disclosure of every possible moiety does not constitute a written description of every species in a genus because it would not "reasonably lead" those skilled in the art to any particular species); In re Ruschig, 379 F.2d 990, 995, 154 USPQ 118, 123 (CCPA 1967).

An applicant may also show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, i.e., complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with

a known or disclosed correlation between function and structure, or some combination of such characteristics.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1 and 20-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is not clear what is meant by functional derivatives or what is the metes and bounds of these functional derivatives.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11 and 20-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mckeage et al. Cancer Chemot. Pharmcol (1995) 36:451-458 in view of Zak et al., US 6,503,943 and Collaueri et al., US 6,221,393 taken with Keppler et al., US 5,256,653 and Calanchi et al. US 5,900,252 as evidence by Swarbrick-Encyclopedia of Pharmaceutical Technology pge 121 ONLY is snagged as placed at the bottom of the action (1998).

Mckeage et al teach instant claim 1 a composition comprising a platinum complex, wherein the complex is JM216 (known as [bis-acetato-amine-dichloro-cyclo-hexaylamine-platinum(IV]) wherein the composition comprises excipients such as microcrystalline cellulose, starch, lactose and magnesium stearate as the slipping agent (using the specification as a dictionary) in the form of capsule, see underlining page 451 and 452 as required in part by instant claims 1, 3 and 5-7. It is noted that the

reference do not teach the instantly claimed compound of claim 4. The reference fails to teach the composition in an excipient formed by granulate with particles smaller than 0.5 mm with atleast one neutral saccharide and atleast one modified polysaccharide.

Zak et al teach a pharmaceutical composition for the therapy of oncological disease containing platinum complex and atleast a pharmaceutical excipient. See col. 3, lines 9-15.

With regard to claims 1 and 4, the platinum complex is (OC-6-43) Bis(acetato)-(1-adamantylamine)-amine-dichloroplatinum, see col. 3, lines 48-51. The reference teaches A is NH3 and A' is an amine group containing 1-18 carbons, B is a carboxylate group, thus the compound 4 and X is halogen, See col. 2, lines 1-30 as required by instant claims 1, 4 and 20-25.

The reference fails to teach the composition in an excipient formed by granulate with particles smaller than 0.5 mm with atleast one neutral saccharide and atleast one modified polysaccharide.

Collaueri et al. teach granules entering into pharmaceuticals compositions are advantageously prepared from a polysaccharide having particles less than 100 μM which is less than 0.5 mM, wherein the polysaccharide is mixed with lactose. See col. 2, lines 56-61 and col. 5, lines 37-42. Table 1 teaches the procedure is by wetting. See col.'s 7 and 8. It is also noted that the particle size is based on the release of the active agent over the desired period of time. See col. 3, lines 34-65.

Keppler et al. teach platinum complexes compositions with regards to instant claims 2, 11 the concentration of the excipients is based on the concentration of the

active agent by weight of the total concentration, thus within the purview of one of ordinary skill in the art to modify. Also the reference teaches tablets can be made with coating materials and that brings the de4layed dissolution and absorption of the pharmaceutical in the gastrointestinal tract so that improved tolerability, protraction or delayed action is achieved. See col. 7, lines 45-50 and col. 8, lines 57-67. Please note that lactose (a neutral saccharide, maize starch and gum) are taught as of the excipients used. It is the understanding that as explained in the art, tablets care coated and because of the type of release pattern the tablet coating will have substance enabling the enterosolvent dissolution in the bowel as taught by Keppler et al. see col. 8, lines 57-67 as required by instant claims 8-9.

Calanchi et al. teach a targeted coated drug release formulation having 0.1 mm size for delivery of drugs to the intestinal comprising metacrylic acid, cellulose acetate, see col. 2, lines 38-60 and col. 3, lines 5-42 as required by instant claims 10-11. The reference teaches coating tablets with membrane that are pH dependent remains intact in the stomach and first part of the intestine while it dissolves when it reaches the disirable pH. See col. 1, lines 57-67.

It would have been obvious to one of ordinary skill in the art to formulate a pharmaceutical composition to comprise excipeints such as lactose and starch because similar formulation have been used in the prior art by Mckeage et al. See underlining page 452. One of ordinary skill in the art would expect the compounds of instant claims 1, 4 and 20 to function the same as that of Mckeage et al. because the only difference is the substitution of the adamantly amine at A' which is within the specie selection of

instant claim 1. Also one of ordinary skill in the art would have been motivated to substitute the Mckeage compound with that of Zak because Zak et al teach the instantly claimed compound and would expect the compound to be capable of forming a granulate with acceptable pharmaceutical excipients having size smaller than 0.5 mm when a polysaccharide and an excipient is used as taught by Collaueri et al. Complex of platinum have been used with excipient such as lactose and starch in the prior art prior to the claimed invention. Taking into account the teaching of Collaueri et al, that granules entering into pharmaceuticals compositions are advantageously prepared from a polysaccharide having particles less than 100 μM which is less than 0.5 mM, It would have been obvious to one of ordinary skill in the art to combine the teachings and formulate a phamaceutical with the claimed characteristics based on the form of release of the active agent. The excipients as taught by Encyc. Pharm. Tech teaches wet granulation having size of 0.5-1.5 mm for the process of producing tablets to improve the flow property as discussed already above (release rate). Therefore one of ordinary skill in the art would have been motivated to have the excipients in a particle size of 0.5 mm or less because particle size is based on the rate of release of the active agent.

One of ordinary skill in the art would have been motivated to add other excipients as a coating agent because based on the type of disease as taught by Calanchi et al. it is important that drugs are transported intact to the place in which they will carry their pharmacological action, therefore necessary to delay the release . See also col. 2, lines 1-5. Therefore the combined art are well within the purview of one of ordinary skill in the art to make a pharmaceutical composition of instant claim 4 for example that is of a

delayed release character having small size because it is taught that the smaller the units are the Wider the distribution in the gastrointestinal tract. See col. 2, lines 38-47 of Calanchi et al.

With regards to the specific concentrations of the excipients as required by instant claims 2 and 9-11, the determination of a dosage having the optimum therapeutic index is well within the level of the ordinary skill in the art, and the artisan would be motivated to determine the optimum amounts to get the maximum effect of the drug, hence the reference makes obvious the instant invention.

It is noted that In re Best (195 USPQ 430) and In re Fitzgerald (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter which there is reason to believe inherently includes functions that are newly cited or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that the subject matter shown to be in the prior art does not possess characteristic relied on" (205 USPQ 594, second first full para.).

Claims 12-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mckeage et al. Cancer Chemot. Pharmcol (1995) 36:451-458 in view of Zak et al., US 6,503,943 and Collaueri et al., US 6,221,393 taken with Keppler et al., US 5,256,653 and Calanchi et al. US 5,900,252 as evidence by Swarbrick-Encyclopedia of Pharmaceutical Technology pge 121 ONLY is snagged as placed at the bottom of the action (1998) as applied to claims 1-11 and 20-25.

The above references are applied here below in there entirety.

Keppler et al. further teach pharmaceuticals are prepared by wet mixing the active substance with the pharmaceutical vehicles , can be dispersed into capsules and the coating are with inert closing layer that enables the control release of the active substance as required by instant claims 12-19. See col. 7, lines 41-49, col. 8, lines 57-67, col. 9, lines 4-15. It is obvious that the formation of tablet is by compression, thus the use of an equipment.

For the same reason given above, one of ordinary skill in the art would have been motivated to manufacture a pharmaceutical composition containing platinum complexes having the characteristics of granules smaller than 0.5 mm prepared by wet granulation that is capable of having a control release formulation.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim **1-25** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1 - 12** of U.S. Patent Application No. **11574775**. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

- Both sets of claims refer to a pharmaceutical composition a mixture of platinum complex of general formula, as recited, with at least one neutral saccharide and one excipient; The scope of the claims of the co-pending application are drawn similarly to the same oral pharmaceutical composition comprising a mixture of platinum complex of general formula, as recited, with at least one neutral saccharide and a modified polysaccharide.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

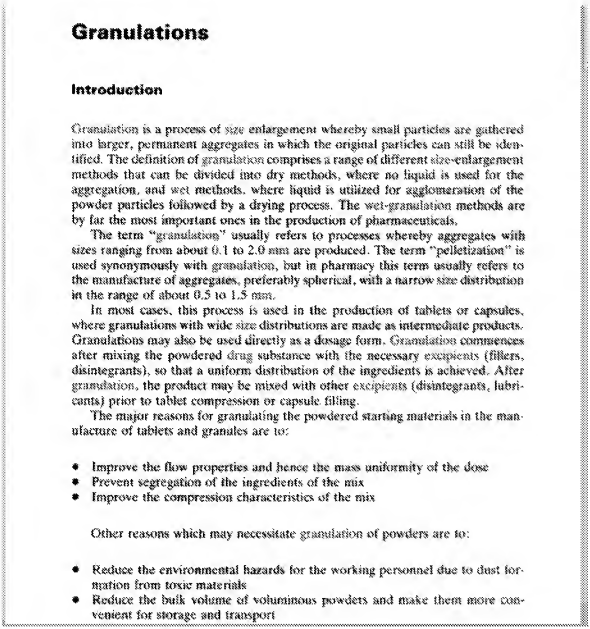
Claim **1-25** are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-7 and 13- 19** of U.S. Patent Application No. **11574929**. Although the conflicting claims are not identical, they are not patentably distinct from each other. The reasons are as follows:

- Both sets of claims refer to a pharmaceutical composition a mixture of platinum complex of general formula, as recited, with at least one neutral saccharide and one excipient; The scope of the claims of the co-pending application are drawn similarly to the same oral pharmaceutical composition comprising a mixture of platinum complex of general formula, as recited, with at least one neutral saccharide and a modified

polysaccharide. The composition would have resulted from the manufacturing process of the instantly claimed process of claims 12-19.

In view of the foregoing, the copending application claims and the current application claims are obvious variations.

No claim is allowed.



Granulations

Introduction

Granulation is a process of size enlargement whereby small particles are gathered into larger, permanent aggregates in which the original particles can still be identified. The definition of granulation comprises a range of different size-enlargement methods that can be divided into dry methods, where no liquid is used for the aggregation, and wet methods, where liquid is utilized for agglomeration of the powder particles followed by a drying process. The wet-granulation methods are by far the most important ones in the production of pharmaceuticals.

The term "granulation" usually refers to processes whereby aggregates with sizes ranging from about 0.1 to 2.0 mm are produced. The term "pelletization" is used synonymously with granulation, but in pharmacy this term usually refers to the manufacture of aggregates, preferably spherical, with a narrow size distribution in the range of about 0.5 to 1.5 mm.

In most cases, this process is used in the production of tablets or capsules, where granulations with wide size distributions are made as intermediate products. Granulations may also be used directly as a dosage form. Granulation commences after mixing the powdered drug substance with the necessary excipients (fillers, disintegrants), so that a uniform distribution of the ingredients is achieved. After granulation, the product may be mixed with other excipients (disintegrants, lubricants) prior to tablet compression or capsule filling.

The major reasons for granulating the powdered starting materials in the manufacture of tablets and granules are to:

- Improve the flow properties and hence the mass uniformity of the dose
- Prevent segregation of the ingredients of the mix
- Improve the compression characteristics of the mix

Other reasons which may necessitate granulation of powders are to:

- Reduce the environmental hazards for the working personnel due to dust formation from toxic materials
- Reduce the bulk volume of voluminous powders and make them more convenient for storage and transport

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SHIRLEY V. GEMBEH whose telephone number is (571)272-8504. The examiner can normally be reached on 8:30 -5:00, Monday- Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

SVG
4/15/08

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614